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Prodrug

Introduction

- The drug gives pharmacologic response by binding with receptor at the site of action.
- There is a factor that limits its optimum entering into this site is considered as barrier.
- The barrier can be overcome by chemically linking promoiety to form prodrug which undergoes biotransformation to release the parent drug which gives the pharmacologic response.

- The term prodrug was first coined by Albert in 1958. Harper (1959) has promoted this concept by defining the term "DRUG LATENIATION" as the chemical modifications of a biologically activity compound to form a new chemical entity, the prodrug.

- The drug is only identified as a prodrug after extensive drug metabolism studies "Serendipity"

- Currently, 5–7% of the drugs approved worldwide can be classified as prodrugs, and approximately 15% of all new drugs approved in 2001 and 2002 were prodrugs. by: Dr. Ali Gamal Al-kaf-Editorial board member of American Medicinal Chemistry Journal. Associate prof. of Med.Chem. Sana’a University. Faculty of Pharmacy. Medicinal Chemistry Department.
Prodrug Terms

- prodrug
- Non-prodrug
  - Hard
  - Soft
  - antedrug
**Initial definitions:**

**Prodrug:**

A pharmacologically inactive compound that is converted to an active drug by a metabolic biotransformation.

✓ “**Soft Drugs**” : These are the opposite of prodrugs. These compounds are designed and synthesized as active compounds that readily undergo metabolic inactivation to nontoxic products.
   Ex: Insulin.

✓ “**Hard Drugs**” : compounds having high lipid solubility or high water solubility having long biological half-life and not susceptible to metabolism.
   Due to their avoiding to metabolism, they have high efficiency but less readily eliminated due to lack of metabolism.
   Ex: Cocaine and heroin.

✓ “**Antedrug**”: compounds that are designed and synthesized to exert their pharmacological activity “**locally**” and when enter the systemic circulation must to be susceptible to metabolic or chemical transformation to inactive compound
   (e.g. steroidal drug that used topically to treat some allergic condition)
## Classification of prodrugs

<table>
<thead>
<tr>
<th>Type</th>
<th>Converting site</th>
<th>Subtype</th>
<th>Tissue location of conversion</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Intracellular</td>
<td></td>
<td>Therapeutic target tissues/cells</td>
<td>Zidovudine, 5-Flourouracil</td>
</tr>
<tr>
<td>Type I</td>
<td>Intracellular</td>
<td>Type IB</td>
<td>Metabolic tissues (liver/lung etc)</td>
<td>Captopril, Cyclophosphamide</td>
</tr>
<tr>
<td>Type II</td>
<td>Extracellular</td>
<td>Type IIA</td>
<td>GI fluid</td>
<td>Sulfasalazine, Loperamide oxide</td>
</tr>
<tr>
<td>Type II</td>
<td>Extracellular</td>
<td>Type IIB</td>
<td>Systemic circulation</td>
<td>Fosphenytoin, Bambuterol</td>
</tr>
</tbody>
</table>
Why use prodrugs?

Prodrugs are used when drugs have unattractive physicochemical properties ((undesirable properties)).

1. Poor aqueous solubility.
2. Low lipophilicity.
3. Chemical instability.
4. Poor patient acceptability.
5. Formulation problems.
8. Not site-specific.
**Prodrug Concept**

Prodrug

- The drug–promoiety is the prodrug that is typically pharmacologically inactive.

- limitation of a parent drug that prevents optimal (bio)pharmaceutical or pharmacokinetic performance.

- The drug and promoiety are covalently linked via bioreversible groups that are chemically or enzymatically labile,
Ideal Property Of Prodrug:

1) The prodrug should be less toxic than the drug.

2) The prodrug should be inactive or significantly less active than the parent drug.

3) The rate formation of drug from the prodrug should be rapid enough to maintain the drug’s concentration. With its therapeutic window.

4) The metabolites from the carrier should be non-toxic or have a low degree of toxicity.

5) The prodrug should be site specific.
Limitation Of Prodrug:

The problem associated with prodrug design is its toxicity which is due to:

- Formation of unexpected metabolite from the total drug conjugates.

- Toxicity may be due to inert carrier generated by cleavage of promoiety and drug conjugate which is converted into toxic metabolite.

- The prodrug might consume a vital cell constituent such as glutathione during its activation stage which causes depletion of prodrug.
Common functional groups on parent drugs that are amenable to prodrug design (shown in green).
**Related definitions**

- **Double Prodrug or pro-prodrug:**
  The double prodrug is a biologically inactive molecule which is transformed in vivo in two steps (enzymatically or chemically) to the active species.

  - **Carrier linked prodrug subdivided into:**
    A. **bipartate**: in which the parent drug is attached to directly to promoiety.
      - comprised of one carrier attached to drug.
    B. **tripartite prodrug**: there is a connector group between drug molecule and promoiety.
      - carrier connected to a linker that is connected to drugs.
Ideal Drug Carriers

• Protect the drug until it reaches the site of action.

• Localize the drug at the site of action.
  • Minimize host toxicity.

• Are biodegradable, inert, and nonimmunogenic.

• Are easily prepared and inexpensive.

• Are stable in the dosage form.
• Examples:

**Carboxylic acid and alcohols:**

a) Dipiveferin HCL:
Dipivefrin HCL is a prodrug of epinephrine formed by the diesterification of epinephrine and pivalic acid. The agent of use in the treatment of open angle glaucoma. The increased lipophilicity relative to epinephrine allows the agent to move across the membrane of the eye easily when applied.

![Chemical structures of Dipiveferin HCl, Epinephrine, and Pivalic acid](image-url)
• **Examples:**

**Carboxylic acid and alcohols:**

b) chloramphenicol palmitate:
A prodrug with reduced water solubility. The hydrophobic palmitate ester does not dissolve to any appreciable extent in the mouth and therefore does not interact with taste receptors.

\[
\text{H NH COCHCl}_2 \quad \text{Esterase} \quad \text{OH OH}
\]

\[
\text{O}_2\text{N – C – C – CH}_2\text{OCO (CH}_2\text{)}_{14}\text{CH}_3
\]

chloramphenicol palmitate

\[
\text{OH OH}
\]

\[
\text{Cl Cl}
\]

chloramphenicol

\[
\text{HC-C}
\]

palmitic Acid
Hetacillin:

Hetacillin is a beta-lactam. Hetacillin is an activity, but is converted by the body to ampicillin, which is active against a variety of organisms.

The effect of forming the Mannich base is to lower the basicity of the amine and thereby increase lipophilicity and absorption.
**Examples:**

* Azo linkage

Sulfasalazine:

- is used in the treatment of *inflammatory bowel disease* (*ulcerative colitis*).
- Anaerobic bacteria in the lower bowel metabolically reduce sulfasalazine to the therapeutic agent **5-aminosalicylic acid**.

![Azo reductase reaction]

Sulfasalazine \(\rightarrow\) Sulfapyridine + 5-aminosalicylic acid
• Examples:

**Carbonyl compounds**

**Methenamine:**
Methanamine is prodrug in acidic pH, methamine is converted to formaldehyde, which act as an antibacterial agent.

\[
\text{Acidic urine pH} \quad \xrightarrow{\text{}} \quad 6 \text{CHO} + 4 \text{NH}_3
\]
• **Examples:**

**Bioprecursor Prodrug**
Which result from a molecular modification of the active compound itself. This modification generates a new compound, which acts as a substrates for the metabolizing enzymes, and metabolite being the expected active agent.

**Nabumetone:** (NSAID) (Relafen) prodrug that requires oxidative activation.
Nabumetone contains no acidic functionality and passes through the stomach without producing the irritation normally associated with this class agent. Subsequent absorption occurs in the intestines.

![Chemical structure of Nabumetone and its active form](image)
• **Examples:**

**Bioprecursor Prodrug**

**Mitomycine C:** Mutamycin® (antineoplastic agent) prodrug that requires Reduction of the **quinone to hydroquinone.**

✓ is a potent **DNA crosslinker.** This crosslink has shown to be effective in killing bacteria.

✓ **Mitomycine C** required a reductive activation followed by two **N-alkylations** specific for a **guanine nucleoside.** Potential bis-alkylating heterocyclic quinones were synthetised in order to explore the antitumoral activities of bacteria.
**Examples:**

**Bioprecursor Prodrug**

*Mitomycine C: Mutamycin®* (antineoplastic agent) prodrug that requires Reduction of the quinone to hydroquinone.

A quinone - electron withdrawing

A hydroquinone - electron donating

Further alkylation

Electrophile

Reduction

- OCH₃

-H⁺
• **Examples:**

**Bioprecursor Prodrug**

**Vidarabine**: (antiviral agent) prodrug that **requires phosphorylation**.

- works by interfering with the synthesis of **viral DNA**.

- vidarabine is sequentially phosphorylated by kinases to the triphosphate **ara-ATP** (active form). This active form is both an inhibitor and a substrate of viral DNA polymerase.

- **ara-ATP** competitively inhibits **dATP** leading to the formation of ‘faulty’ viral DNA.
• **Examples:**

**Bioprecursor Prodrug**

Vidarabine: (antiviral agent) prodrug that requires phosphorylation.
• **Examples:**

**Mutual Prodrug**

Prodrug comprises of two pharmacologically active agents coupled together to form a single molecules such that each act as the carrier for the other prodrug of two active compounds are called as mutual prodrug.
• **Examples:**

**Mutual Prodrug**

**Estramustine:**

✓ **Used for the** treatment of progressive carcinoma of the prostate.

✓ Prodrug is selectively taken up into estrogen receptor positive cells then linkage is hydrolyzed.

\[
\text{Estramustine Sodium Phosphate} \quad \text{Emcyt® - Pharmacia & Upjohn}
\]

17-alphaestradiol slow prostate cell growth
Nornitrogen mustard is a weak alkylating agent
DIPIVEFRIN HCl 0.1%, Alcon® ophthalmic solution contains 125mg of Chloramphenicol Palmitate.

KLORAN SUSPENSION contains 125mg of Chloramphenicol Palmitate.

Hetacin-K

Relafen®
Mandelamine ®
(methenamine)

Sultamicillin ®
(Sultamacillin)
(a) PHARMACEUTICAL APPLICATIONS

- **Improvement of taste.**
  
  Ex: Parent drug: Chloramphenicol, Prodrug: Palmitate ester

- **Improvement of odor.**
  
  E.g.; Ethyl mercaptan which is a foul smelling liquid, is converted into its drug ester, which has higher b.p. and odorless.

- **Reduction of pain on injection.**
  
  E.g. the low aqueous solubility of clindamycin HCl is responsible for pain on injection. This can be overcome by use of more water soluble prodrugs of such agents. E.g. 2-phosphate ester of clindamycin.

- **Enhancement of drug solubility and dissolution rate (hydrophilicity of drug).**

- **Enhancement of chemical stability of drug.**
  
  Ex: Formaldehyde is used as prodrug ((methenamine)) in the form of enteric coated to prevent hydrolysis in the stomach. ((urinary tract antiseptic)).
(b) PHARMACOKINETIC APPLICATIONS

• Enhancement of bioavailability (lipophilicity).

• Prevention of presystemic metabolism.

• Prolongation of duration of action.

• Reduction of toxicity.

• site-specific drug delivery (drug targeting).
Examples of Prodrugs for improved lipophilicity or permeability
Prodrug

MGS0210 in monkeys increased to 44% for
MGS0039 in monkeys increased to 13% for

Bioconversion by esterases

The oral bioavailability of less than 1% for

n-Hep/ester of

MGS0039

Prodrug

Ximelegatran 9.96%
melagatran increased to 20% for
The oral bioavailability of 3-7% for
enzymes

Bioconversion by esterases and reductive

Ximelegatran

Melagatran
and ethyl ester of
Hydroxyaminidine (anticoagulant)
(Ximelegatran)
Examples of Prodrugs for improved aqueous solubility
A commercial parenteral produg

consequence of the prior existence of

phthalazine may have only been as

parent drug development or an oral produg

Based on a modest advantage over the

marketed only for parenteral use

Until recently, phthalazine phosphate was

Biocconversion by alkaline phosphatases

Treatment

Children's compliance to prednisolone

a liquid formulation, and thus, improved

The produg enabled the development of

Biocconversion by alkaline phosphatases

carcinoma since the mid-1970s. Prostate

formulations for the treatment of prostate

Marked both as injectable and oral

Biocconversion by alkaline phosphatases
Examples of Prodrugs for improved parenteral administration
<table>
<thead>
<tr>
<th>Prodrug Strategy</th>
<th>Prodrug Name</th>
<th>Structure</th>
<th>Functional Group</th>
<th>Therapeutic Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prodrug for Improved Parenteral Administration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Solubility of propofol from 150 mg per ml
- Significantly increased the aqueous solubility of propofol
- Intravenous administration by a saline
- Is rapidly converted to propofol after

- Fosphenylpropanoic (over 300 mg per ml)
- Increased aqueous solubility of administration
- Higher dose product for intravenous administration
- Allows a low-volume bolus and phosphate
- Bioconversion by alcohol

- Per ml of fosphenytoin
- 20-25 mg per ml of phenytoin to 140 mg
- Increased aqueous solubility from 7-15 min
- Alcohol-phenytoin (half-life, lives
- Rapidly converted to phenytoin by
Only the lactone form is active.

 equilibrium with closed and open forms

 undergoes rapid, pH-dependent

 ng per ml (at pH 3-4) of inotecan

 per ml (in water) of camptothecin to 20

 Increased aqueous solubility from 2-3 μg

 phosphonoxy methyl prodrug

 significantly lower when compared with

 after intravenous administration is

 But bioconversion to prodrug

 solubility of prodrug (150 μg per ml)

 Significantly increased the aqueous

 Prodrug

 (anesthetic)

 Phosphate

 (antitumor)

 Prodrug

 (anesthetic)
Examples of Prodrugs to exploit carrier-mediated absorption
<table>
<thead>
<tr>
<th>Prodrug Strategy</th>
<th>Structure</th>
<th>Functional Group</th>
<th>Name (therapeutic area)</th>
</tr>
</thead>
<tbody>
<tr>
<td>valacyclovir</td>
<td><img src="#" alt="Valacyclovir Structure" /></td>
<td>hydrolysis (valacyclovir)</td>
<td>antiviral (antigenic)</td>
</tr>
<tr>
<td>from 12% to 20% (acyclovir) improved</td>
<td>by HPLC</td>
<td>transported predominantly</td>
<td>L-valyl ester</td>
</tr>
</tbody>
</table>

Prodrug to exploit carrier-mediated absorption
Examples of Prodrugs for improved ophthalmic and dermal delivery
| Prodrugs for Improved Ophthalmic and Dermal Delivery |

**Product Strategy**

<table>
<thead>
<tr>
<th>Structure</th>
<th>Functional Group</th>
<th>Therapeutic Area</th>
</tr>
</thead>
</table>

- **Prodrug**
  - Skin permeation
  - Improved lipoavailability and bioconversion by esterases
  - Better ocular absorption and bioconversion by esterases
  - Faster than adrenalin (11,920 times)

<table>
<thead>
<tr>
<th>Chemical Structure</th>
</tr>
</thead>
</table>

- Ethyl ester of tazarotene (acne, psoriasis)
- Isopropyl ester of tazarotene (topical skin)
- Acid of latanoprost (glaucoma)
- Diester of latanoprost (glaucoma)
- Diethylaminoethyl ester of dipiverine (glaucoma)
Examples of Prodrugs for other purposes
**Prodrug Strategy**

**Structure**

**Functional Group**

Table 9 | Products for Other Purposes
Prodrug Therapies ((cancer therapies))

For selective activation of prodrugs in tumor cells Two steps

I. incorporate a prodrug-activating enzyme into a target tumor cell.
II. administer a nontoxic prodrug which is a substrate for the exogenous enzyme incorporated.

Criteria for Success with Enzyme-Prodrug Therapies

I. The prodrug-activating enzyme is either nonhuman or a human protein expressed poorly
II. The prodrug-activating enzyme must have high catalytic activity
III. The prodrug must be a good substrate for the incorporated enzyme and not for other endogenous enzymes
IV. The prodrug must be able to cross tumor cell membranes
V. The prodrug should have low cytotoxicity and the drug high cytotoxicity
VI. The activated drug should be highly diffusable to kill neighboring nonexpressing cells (bystander killing effect)
VII. The half-life of the active drug is long enough for bystander killing effect but short enough to avoid leaking out of tumor cells
(a) Antibody Directed Enzyme Prodrug Therapy (ADEPT)
An approach for site-specific delivery of cancer drugs.

I. Phase One:
An antibody-enzyme conjugate is administered which binds to the surface of the tumor cells. The antibody used has been targeted for the particular tumor cell. The enzyme chosen for the conjugate is one that will be used to cleave the carrier group off of the prod rug administered in the next phase.

2. Phase Two:
After the antibody-enzyme has accumulated on the tumor cell and the excess conjugate is cleared from the blood and normal tissues, the prodrug is administered. The enzyme conjugated with the antibody at the tumor cell surface catalyzes the conversion of the prodrug to the drug when it reaches the tumor cell.

Advantages
1. Increased selectivity for targeted cell.
2. Each enzyme molecule converts many prodrug Molecules.
3. The released drug is at the site of action.
4. Demonstrated to be effective at the clinical level.
5. Concentrates the drug at the site of action.

Disadvantages
1. Immunogenicity and rejection of antibody-enzyme conjugate
2. Complexity of the two-phase system and i.v administration
3. Potential for leak back of the active drug
(b) Antibody-Directed Abzyme Prodrug Therapy (ADAPT)

Instead of using a prodrug-activating enzyme, a humanized prodrug-activating catalytic antibody (abzyme) can be used. Ideally, the abzyme catalyzes a reaction not known to occur in humans, so the only site where the prodrug could be activated is at the tumor cell where the abzyme is bound. Antibody 38C2 catalyzes sequential retro-aldol and retro-Michael reactions not catalyzed by any known human enzyme. Found to be long-lived in vivo, to activate prodrugs selectively, and to kill colon and prostate cancer cells.

(c) Gene-Directed Enzyme Prodrug Therapy (GDEPT)

A gene encoding the prodrug-activating enzyme is expressed in target cancer cells under the control of tumor-selective promoters or by viral transfection. These cells activate the prodrug as in DEPT.
Principle of gene-directed enzyme prodrug therapy (GDEPT)

- Tumor cell
- Death of transduced cells
- Death of neighboring cells

- Suicide gene
- Expression of suicide gene
- Suicide enzyme
- Active toxic drug
- Suicide
- Non-toxic prodrug

- Transduction
- Virus encoding suicide enzyme
References:

Medicinal chemistry
Related Journals

- Drug Designing: Open Access
- Biochemistry & Pharmacology
- Advances in Pharmacoepidemiology & Drug Safety
Medicinal chemistry
Related Conferences

- 3rd International Conference on Medicinal Chemistry & Computer Aided Drug Designing
- 3rd International Conference and Exhibition on Pharmacognosy, Phytochemistry & Natural Products
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